

1 **Development of Safety Qualification Thresholds and Their Use in Orally Inhaled and Nasal**
2 **Drug Product Evaluation**

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6 Submitted to *Toxicological Sciences* for consideration as a Review article

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9 Abstract

10 Safety thresholds for chemical impurities and leachables in consumer products such as
11 foods and drugs have helped to ensure public health while establishing scientifically sound limits
12 for identification and risk assessment of these compounds. The Product Quality Research
13 Institute (PQRI) Leachables and Extractables Working Group, a collaboration of chemists and
14 toxicologists from FDA, industry, and academia, has developed safety thresholds for leachables
15 and extractables in orally inhaled and nasal drug products (OINDP), for application in United
16 States pharmaceutical submissions. The PQRI safety concern threshold (SCT) is 0.15 µg/day,
17 and the qualification threshold (QT), 5 µg/day. OINDP are important in the treatment of lung
18 diseases such as asthma and chronic bronchitis, as well as systemic diseases such as diabetes.
19 Analysis of extractables and minimization of leachables in OINDP are vital to ensuring the
20 quality and safety of the final product. It is expected that the thresholds developed by the PQRI
21 Leachables and Extractables Working Group will be used by both industry and regulators to
22 ensure and assess such quality and safety in OINDP applications. In this paper, we describe the
23 importance of the PQRI safety thresholds in the OINDP pharmaceutical development process;
24 the background and context of safety thresholds for consumer products; how these safety
25 thresholds were developed using well-established, robust databases and quantitative risk
26 assessment approaches; and how these thresholds can be applied in a pharmaceutical safety
27 qualification process, including FDA regulatory perspectives on the use of safety thresholds for
28 OINDP.

29 Keywords: qualification threshold, safety concern threshold, leachables, extractables,
30 inhalation, nasal, PQRI

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32 **I. Introduction**

33 **A. Why are extractables and leachables important in inhalation drug product**
34 **pharmaceutical development?**

35 Extractables, as defined by the U.S. Food and Drug Administration (FDA), are
36 compounds that can be extracted from elastomeric components, plastic components, or coatings
37 of the container and closure system when in the presence of an appropriate solvent(s).

38 Leachables are compounds that leach from elastomeric or plastic components or coatings of the
39 container and closure system as a result of direct contact with the drug product formulation

40 (Food and Drug Administration, 1998 and July 2002). Extractables are therefore potential

41 leachables, and patients could be exposed to leachables. Leachables in orally inhaled and nasal

42 drug products (OINDP) are generally considered by pharmaceutical regulatory agencies to be of

43 significant safety concern (FDA, 1999) because for some OINDP, leachables could be delivered

44 directly to the diseased lung. For OINDP, toxicological and chemical assessments of leachables

45 and extractables are a critical part of the pharmaceutical development process. Further,

46 extractables and leachables can often impact on the marketing approval of a drug product.

47 OINDP include nasal sprays and inhalation sprays, metered dose inhaler (MDI) solutions and

48 suspensions, inhalation solutions, and dry powder inhalers (DPIs). These drug products are used

49 to mitigate the effects of indications such as asthma, emphysema, and allergy symptoms, and to

50 deliver medication directly to affected areas such as the nasal passages and lungs (local

51 delivery). Newer inhalation products, such as those for delivery of insulin to treat diabetes, seek

52 to deliver medication throughout the body, via the lungs (systemic delivery).

53 Each inhalation or nasal drug product, includes a container closure system that is a vital

54 part of the drug product as a whole, facilitating drug delivery and protecting the integrity of the

55 formulation. For example, the MDI consists of a solution or suspension formulation (drug
56 substance or active pharmaceutical ingredient; chlorofluorocarbon (CFC) or hydrofluoroalkane
57 (HFA) propellants to facilitate aerosol dose delivery; and surfactants, co-solvents and other
58 excipients to help stabilize the formulation), and a container closure system with various physical
59 components (metal canister to contain the pressurized formulation; a valve to meter the
60 formulation dose to the patient; elastomer components to seal the valve to the can and contain the
61 pressurized formulation; and an actuator/mouthpiece to facilitate patient self-dosing). The
62 formulation and container closure system are closely integrated in the MDI drug product, which
63 is generally true of all OINDP. The container closure systems for OINDP from which leachables
64 may appear can include not only primary packaging components, e.g., canisters for MDIs and
65 blister packages for DPIs, but also secondary packaging, such as overwraps or labels that are not
66 in direct contact with the drug formulation.

67 OINDP container closure systems components can consist of various elastomeric (rubber)
68 and polymeric (plastic) materials. These components can be seals, parts of MDI valves,
69 mouthpieces, etc. All such elastomeric and polymeric materials contain relatively low molecular
70 weight soluble organic chemical entities, either purposefully added to the materials during
71 synthesis, compounding, or fabrication (e.g., polymerization agents, fillers, antioxidants,
72 stabilizers, and processing aids), or present in the materials as a by-product of synthesis,
73 compounding, or fabrication (e.g., oligomers, additive contaminants, and reaction products). All
74 of these chemical entities have the capacity to leach into the formulation and be delivered to the
75 patient. Leachables and extractables represent a variety of chemical types and classes, and
76 leachables can be present in inhalation drug products at widely varying concentrations.
77 Extractables and leachables can also include certain structure types with known safety

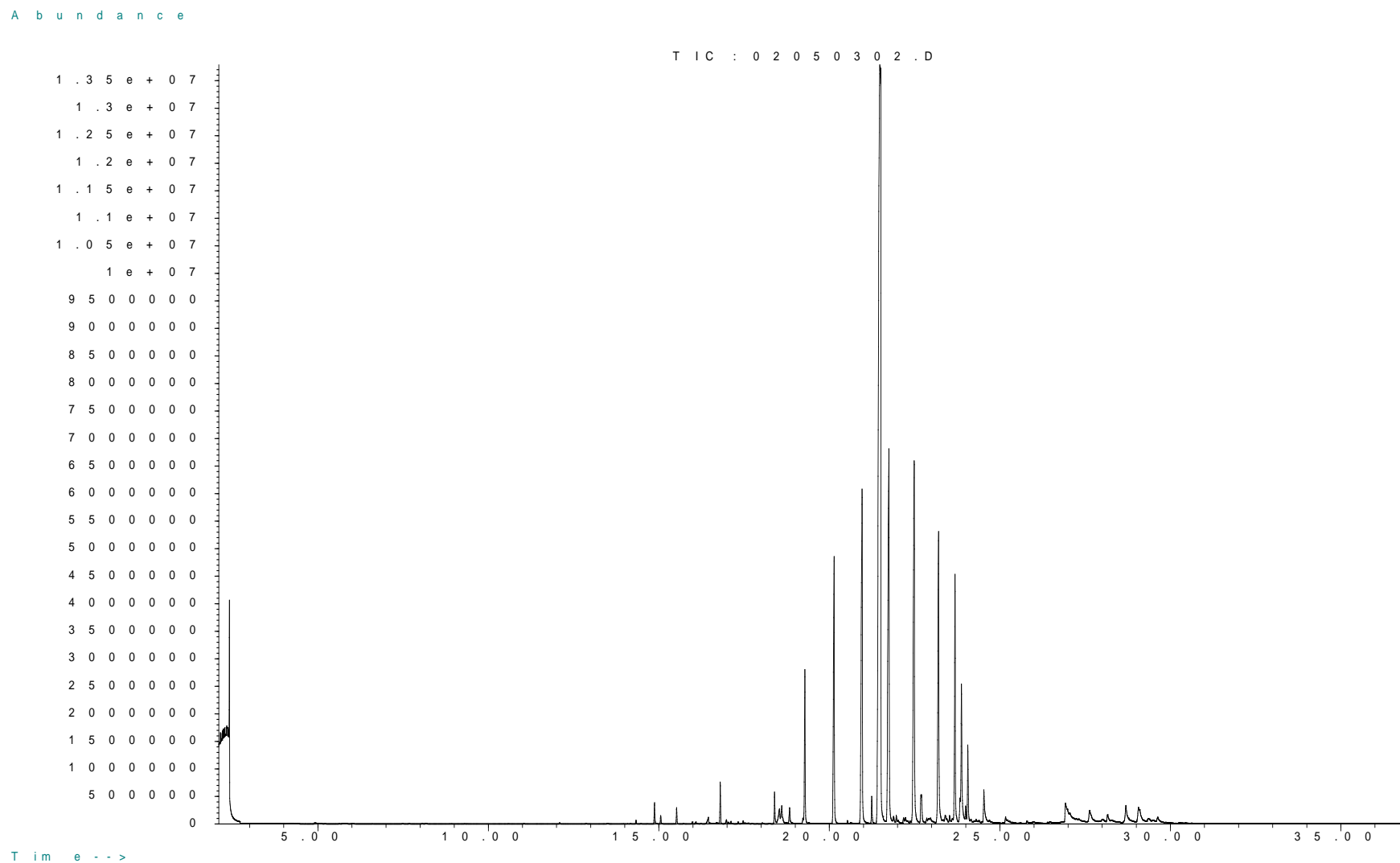
78 implications, such as N-nitrosamines, polyaromatic hydrocarbons (PAHs), and
79 mercaptobenzothiozoles (FDA, November 1998 and July 2002).

80 **B. Why do we need safety thresholds?**

81 Modern analytical chemistry has enormous capability for analyzing extractables and
82 leachables. For example, Gas Chromatography/Mass Spectrometry (GC/MS) and Liquid
83 Chromatography/Mass Spectrometry (LC/MS), are capable of separating, identifying and
84 quantifying highly complex mixtures of organic chemical entities such as those produced from
85 Controlled Extraction Studies of OINDP container closure system components (see Figure 1)
86 (Norwood *et al.*, 2005). These analyses are routinely accomplished at very high sensitivity,
87 easily detecting organic leachables at low $\mu\text{g}/\text{canister}$ levels in MDIs (Norwood *et al.*, 1995).
88 The available scientific literature would indicate that many hundreds, if not thousands, of
89 individual chemical entities that can appear as extractables/leachables could potentially be
90 detected, identified, and quantified at similar levels.

91 However, it is well established that there are levels at or below which organic chemical
92 entities in drug product represent no safety concern to patients. Therefore, the establishment of
93 safety thresholds that are protective of patients for OINDP leachables and extractables can be
94 justified and are believed to be necessary to limit unreasonable and extended evaluations of
95 chemicals present at levels that cannot harm patients. An efficient pharmaceutical development
96 process requires guidance on “how low to go” for the identification and quantification of
97 extractables and leachables.

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Figure 1. A GC/MS extractables “profile” of an elastomer (Total Ion Chromatogram of a solvent extract).

101 To ensure quality and safety of OINDP through knowledge of amounts and types of
102 extractables and leachables, safety thresholds must be applied in conjunction with
103 pharmaceutical development “best practices,” which include safety assessment of potential
104 leachables throughout the development program. Such assessment should include at a minimum:
105 safety evaluation of supplier information during container closure component selection; safety
106 evaluation of potential leachables during Controlled Extraction Studies on OINDP components;
107 safety evaluation of leachables; and safety input to extractables specifications for routine quality
108 control of extractables.

109 **C. The PQRI Leachables and Extractables Effort**

110 In 2001, the Product Quality Research Institute (PQRI) initiated a project to develop
111 safety and analytical thresholds for leachables and extractables in OINDP.¹ At the time there
112 was no regulatory guidance available for such thresholds. Furthermore, International Conference
113 on Harmonisation (ICH) thresholds for impurities are not applicable to leachables and
114 extractables in OINDP (ICH Q3A(R1), 2003; ICH Q3B(R2), 2003; ICH Q3C(R3), 2003).

115 The PQRI Leachables and Extractables Working Group, consisting of toxicologists and
116 chemists from industry, FDA, and academia, developed a safety concern threshold and a
117 qualification threshold for leachables; an analytical evaluation threshold for extractables and
118 leachables; processes for applying these thresholds; and best practices for selecting OINDP
119 container closure system components and conducting Controlled Extraction Studies, leachables
120 studies, and routine extractables testing.

¹ Product Quality Research Institute: <http://www.pqri.org>

121 The PQRI safety concern threshold (SCT) is proposed to be 0.15 µg/day, and the
122 qualification threshold (QT), 5 µg/day. The SCT is the threshold below which a leachable would
123 have a dose so low as to present negligible safety concerns from carcinogenic and
124 noncarcinogenic toxic effects. The QT is the threshold below which a given non-carcinogenic
125 leachable is not considered for safety qualification (toxicological assessments) unless the
126 leachable presents structure-activity relationship (SAR) concerns. Below the SCT identification
127 of leachables generally would not be necessary. Below the QT leachables without structural
128 alerts for carcinogenicity or irritation would not require compound-specific risk assessment.

129 In 2006, the PQRI recommendations were submitted to the FDA for consideration in the
130 FDA's development of regulatory recommendations for OINDP (PQRI, 2006). Safety
131 Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug
132 Products. <http://www.pqri.org>). This paper describes, from a United States perspective,
133 historical background on the development and application of safety thresholds for consumer
134 products; the development and application of the PQRI safety thresholds for leachables in
135 OINDP; and FDA regulatory perspectives on the use of these safety thresholds.

136 I. Concept and History of Safety Thresholds

137 Over five hundred years ago Paracelsus made the astute observation that: "All substances
138 are poisons; there is none which is not a poison. The right dose differentiates a poison from a
139 remedy." A corollary to this bit of wisdom is that for most or perhaps even all toxicological
140 effects, there exist thresholds: a dose below which an exposure imparts no risk. While most
141 toxicologists would likely agree with this principle, the means for calculating the threshold can
142 sometimes be controversial. In addition, for some adverse health endpoints, i.e., mutagenesis
143 and carcinogenesis, most regulatory agencies have assumed a lack of a threshold. Practically,

144 this means that any exposure results in some increased risk for mutation and/or cancer.

145 Nevertheless, it is often impossible to reduce human exposures to zero.

146 Two types of methodologies have evolved in risk assessment: one for calculating safe
147 exposure values for health effects thought to have thresholds, and a second for calculating
148 “virtually safe” exposure values for health effects thought to lack thresholds. In both cases, the
149 method involves extrapolation of agent-induced health effects in animals to human risk. For
150 drug development, methodologies for threshold-associated exposures are discussed in ICH Q3C,
151 Impurities: Guideline for Residual Solvents (ICH Q3C(R3), 2003). The guideline discusses a
152 method for calculating a PDE, “permissible daily exposure” to a residual solvent. Calculating
153 PDEs for mutagenic and carcinogenic substances is more complex. In this case, a “virtually safe
154 dose” can be established, using animal studies, as a dose that implies a negligible risk when
155 administered over a lifetime. A virtually safe dose has been defined somewhat differently by
156 different regulatory agencies. In general, however, it refers to lifetime exposures that increase
157 the risk of cancer by either one in one million or one in one hundred thousand.

158 These types of risk assessments are often used to calculate acceptable levels of
159 carcinogens in drinking water, air, and soil at hazardous waste sites. In order to perform such
160 risk assessments, data from rodent lifetime bioassays are required. Data from such studies are
161 often not available for impurities found in drug substances and drug products, and because of the
162 resource intensity and protracted nature of rodent lifetime bioassays, it is generally not practical
163 to test all potentially carcinogenic impurities in such an assay. This conundrum has led
164 toxicologists to devise the concept of the “threshold of toxicological concern” (TTC) (Kroes, *et*
165 *al.*, 2004). These authors define the TTC as “a level of exposure for all chemicals, whether or
166 not there are chemical-specific toxicity data, below which there would be no appreciable risk to

167 human health.” The concept of a TTC appears to have originated with FDA’s threshold of
168 regulation for indirect food additives (FDA, 1995).

169 In general, an impurity exposure level of 1.5 µg/person/day is considered an acceptable
170 threshold below which further qualification for genotoxicity/carcinogenicity concerns would not
171 be required. The qualification threshold was originally developed as a “threshold of regulation”
172 by the Center for Food Safety and Applied Nutrition (CFSAN) at the FDA for food contact
173 substances and was further standardized by the CFSAN/FDA in a companion guidance document
174 for food contact substances (FDA, 1995 and April 2002). Substances with no known cause for
175 concern that may migrate into food are exempted from regulation as a food additive if present at
176 daily dietary concentrations at or below 0.5 parts per billion, corresponding to 1.5 µg/person/day
177 based on a total daily consumption of 3 kg of solid and liquid foods. The threshold is an estimate
178 of daily exposure expected to result in an upper bound lifetime risk of cancer of less than 10⁻⁶,
179 considered a “virtually safe dose”. The initial CFSAN/FDA analysis was based on an
180 assessment of 343 carcinogens from a Carcinogenic Potency Database (CPDB) and was derived
181 from the probability distribution of carcinogenic potencies of those compounds (FDA, 1995;
182 Gold *et al.*, 1984; Rulis, 1992). Subsequent analyses of an expanded database of more than 700
183 carcinogens further confirmed the threshold (Fiori and Meyerhoff, 2002). Additional analysis of
184 subsets of highly potent carcinogens suggested that a threshold of 0.15 µg/day, corresponding to
185 a 10⁻⁶ lifetime risk of cancer, may be more appropriate for chemicals with structural alerts for
186 potential genotoxicity (Kroes *et al.*, 2004). Some structural groups including aflatoxin-like-, N-
187 nitroso-, and azoxy-compounds were identified to be of extremely high potency and are excluded
188 from the threshold approach.

189 United States federal regulatory agencies such as the EPA and FDA typically use a 10^{-6}
190 lifetime risk of cancer to determine “acceptable” risk from chemical exposures, although higher
191 risk levels are accepted under certain circumstances, namely for active pharmaceutical
192 ingredients from which a benefit may be derived. This level of exposure is expected to produce
193 a negligible increase in carcinogenic risk based on the analysis of the CPDB. Additionally, this
194 threshold is considered to be low enough to ensure that the presence of an unstudied compound
195 that is below the threshold will not significantly alter the risk/benefit ratio of a drug product,
196 even if the impurity is later shown to be a carcinogen.

197 In developing the SCT and QT, the PQRI Working Group carefully considered the
198 assumptions, approaches and, where possible, exposure data used in developing the threshold of
199 regulation for food additives, the TTC, and ICH thresholds for impurities. The Working Group
200 took a relatively conservative approach in the assumptions applied to development of the SCT
201 and QT. These assumptions were in many cases different than those used in development of
202 these other thresholds, taking into account the possibility of mixtures of leachables, and a real
203 potential for the presence of carcinogenic leachables. Further, unlike impurities, which are
204 associated with drug substance or drug product, leachables are not drug related and could possess
205 different toxic characteristics. The approaches to and assumptions made in establishing the SCT
206 and QT are explained below.

207 **III. Safety Thresholds for Leachables in OINDP**

208 Because leachables originate in the container closure system rather than the synthetic
209 pathway, the PQRI SCT and QT are based solely on $\mu\text{g}/\text{day}$ intake of leachables, unlike ICH
210 thresholds for drug product impurities, which are linked to the dose of the active pharmaceutical
211 ingredient. The PQRI thresholds were defined in relation to estimated safe human inhalation

212 exposures for sets of chemicals assessed for different toxicity endpoints, an approach similar to
213 that used by others to determine thresholds for orally ingested substances (Blackburn *et al.*,
214 2005; Cheeseman *et al.*, 1999; Dolan *et al.*, 2005; Fiori and Meyerhoff, 2002; Kroes *et al.*, 2000;
215 Kroes *et al.*, 2004; FDA, 1995; Munro *et al.*, 1996; Rulis, 1992).

216 **A. Derivation of the Safety Concern Threshold (SCT)**

217 The SCT is based on carcinogenicity endpoints because carcinogenic effects occur at
218 lower intakes than those associated with noncarcinogenic toxicity. This was previously
219 demonstrated for orally ingested compounds, including those with potent neural, reproductive, or
220 endocrine toxicity (Kroes *et al.*, 2000). Our analysis confirms that genotoxic carcinogenicity is a
221 concern at lower doses of inhaled compounds than acute respiratory irritation, or chronic
222 respiratory and systemic toxicity.

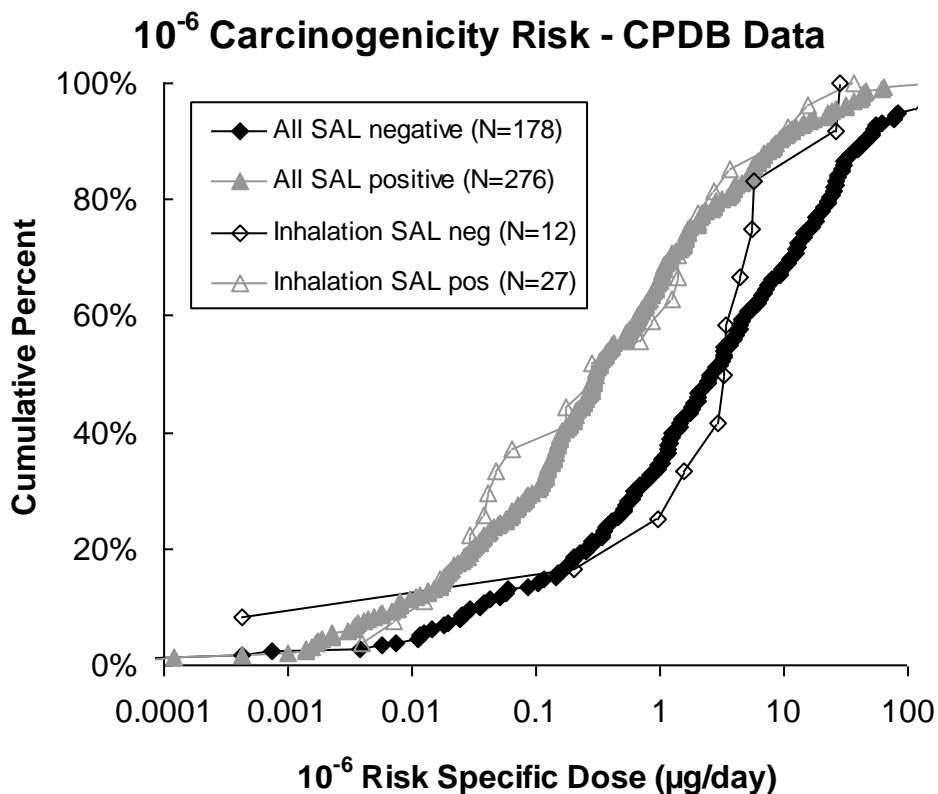
223 The Working Group based the SCT on the potencies of genotoxic carcinogens (i.e.,
224 positive for mutations in *Salmonella*, SAL+) in the Carcinogenic Potency Database (CPDB),
225 which expresses carcinogenic potency as the TD50, the daily dose inducing a particular tumor
226 type in half of the animals that otherwise would not develop the tumor over a lifetime. Human
227 10^{-6} risk specific doses were estimated by linear extrapolation from the TD50 (Blackburn *et al.*,
228 2005; Cheeseman *et al.*, 1999; Fiori *et al.*, 2002; Krewski *et al.*, 1990; Kroes *et al.*, 2004; Rulis,
229 1992). As expected (Cheesman *et al.*, 1999), SAL+ carcinogens are more potent carcinogens
230 (Figure 2). The SAL+ compounds are also appropriate for establishing a threshold for structural
231 identification because structural alerts are more predictive for SAL+ than for nongenotoxic
232 carcinogens (Benigni and Zito, 2004). Furthermore, most known human carcinogens are
233 genotoxic (Bartsch and Malaveille, 1989), and the assumption of linear extrapolation of cancer
234 risk is more appropriate for SAL+ compounds than for nongenotoxic compounds, which may

235 exhibit mechanism-based thresholds for tumorigenesis. Too few inhalation studies were
236 represented in the CPDB to establish a threshold based solely on inhalation data. However, the
237 potency of carcinogens tested by inhalation mirrors that of those tested by all routes (Figure 2);
238 thus data from all routes should be representative of inhalation carcinogens.

239 A 10^{-6} risk specific dose was used as a negligible carcinogenicity risk in our analysis,
240 consistent with the threshold of regulation for indirect food additives (FDA, 1995). The
241 relatively conservative 10^{-6} risk level was considered an appropriate starting point for
242 identification and evaluation of leachable impurities because it is not uncommon for there to be a
243 mixture of multiple leachable impurities with potential genotoxicity issues in an OINDP, and
244 there are examples of potent carcinogens found as leachables in OINDP.

245 Our estimates of human 10^{-6} risk specific doses included allometric scaling factors, based
246 on default body weights (70-kg human, 350-g rat, 30-g mouse) to the 0.75 power, used by the
247 U.S. Environmental Protection Agency (EPA, 1992). In U.S. pharmaceutical labeling, dose
248 metrics from carcinogenicity assays are typically scaled to body surface area on a mg/m^2 basis
249 (default body weight to the 2/3 power). **These two specific dose-scaling approaches result in**
250 **relatively small (<2-fold) differences in human dose estimates (FDA, 2005), considering that**
251 **carcinogen potencies range over several orders of magnitude.** Because applying multiple
252 conservative assumptions can unrealistically overestimate carcinogenic risk (Gaylor *et al.*, 1993),
253 the Working Group used a central estimate of risk rather than an upper-bound 95% risk estimate,
254 and used the geometric mean of potencies from rats and mice rather than using the most sensitive
255 species. Based on these assumptions, the median human equivalent 10^{-6} risk specific dose for
256 SAL+ carcinogens in the CPDB is $0.36 \mu\text{g}/\text{day}$, and the median excess cancer risk at the SCT of
257 $0.15 \mu\text{g}/\text{day}$ is 0.41×10^{-6} . If <20% of random chemicals are genotoxic carcinogens (Fung *et al.*,

258 1995; Sawatari *et al.*, 2001), <7% of all compounds would exceed 10^{-6} increased cancer risk at
 259 lifetime intakes <0.15 $\mu\text{g}/\text{day}$. Thus, a leachable below the SCT is unlikely to have a lifetime
 260 excess cancer risk $>10^{-6}$, and identification of leachables below this threshold generally would
 261 not be necessary.



262

263 **Figure 2.** Carcinogenic potency of genotoxic (SAL-positive) and non-genotoxic (SAL-negative)
 264 carcinogens from the Carcinogenic Potency Data Base (CPDB) from studies conducted in
 265 rodents by inhalation or all routes combined.

266

267 B. Derivation of the Qualification Threshold

268 The Qualification Threshold is based primarily on regulatory agency "reference doses"
 269 derived by applying safety factors to no-observed-adverse-effect levels (NOAELs) for
 270 noncarcinogenic toxicity. The Working Group analyzed 150 inhaled compounds with "Chronic
 271 Reference Doses"(RfDs) established by the US EPA, "Minimum Risk Levels" (MRLs)

272 established by the US Agency for Toxic Substances and Disease Registry, or "Reference
273 Exposure Levels" (RELs) established by the California EPA. The median reference values were:
274 120 µg/day (10th percentile = 1.5 µg/day) for chemicals with reference values based on
275 respiratory toxicity, and 1940 µg/day (10th percentile = 5.0 µg/day) for chemicals with systemic
276 toxicity endpoints. Based on the large safety margins (~100-fold) incorporated in reference
277 doses, leachables at intakes <5 µg/day should pose negligible health risks. Compounds with
278 respiratory toxicity and inhalation reference values less than 5 µg/day are dominated by metals
279 and metal salts, and by reactive compounds with readily identifiable structural alerts for irritant
280 potential, such as aldehydes and isocyanates.

281 In developing the QT, the Working Group focused on the total inhaled dose, which
282 assumes 100% deposition, rather than on the actual dose deposited in the lungs. The 5 µg/day
283 QT therefore represents a small percentage - between only 1% and 6% - of the quantity of
284 particulate that individuals are normally inhaling. Note that these percentages would be even
285 smaller if comparison were made to, for instance, air concentrations equal to the National
286 Ambient Air Quality Standard for the respirable fraction (PM₁₀), which is considered protective
287 of public health including sensitive sub-populations.

288 The Working Group also considered acute respiratory irritation in relation to the
289 Qualification Threshold, since potential airway irritation and bronchoconstriction are concerns
290 for impurities in OINDP (Shaheen *et al.*, 1994). A useful metric of sensory irritation is the
291 RD50, the concentration of an irritant that decreases respiratory frequency by 50% in mice
292 (Alarie *et al.*, 1980). A good correlation was reported between occupational threshold limit
293 values and the value of $0.03 \times \text{RD50}$ (Schaper, 1993). To estimate safe doses for respiratory
294 irritants, the Working Group calculated the µg dose at the RD50 concentration inhaled for

295 10 minutes divided by 1000 for a large set of chemicals (Schaper, 1993). The additional 30-fold
296 safety margin for this metric, compared to the value of $0.03 \times \text{RD50}$, should be sufficient to
297 account for sensitive populations such as asthmatics as illustrated in Table 1. The distribution of
298 $\text{RD50}/1000$ doses was quite similar to the distribution of NOAELs for chronic respiratory
299 toxicity. As with the chronic respiratory toxicants, compounds with $\text{RD50}/1000$ values below
300 the $5 \mu\text{g}/\text{day}$ were predictably irritant compounds such as aldehydes, isocyanates, and nitriles.

301 Pediatric populations were also considered. Children would be adequately protected by
302 the proposed QT since it is based upon inhalation reference values that are intended to protect
303 essentially all people, including sensitive subpopulations such as children. When establishing
304 RfD and RfC values, the EPA identifies the NOEL, lowest-observed-adverse-effect-level
305 (LOAEL), or benchmark dose or concentration and then divides this value by a series of
306 uncertainty factors. One uncertainty factor relevant to children accounts for variability in toxic
307 response among people, including highly sensitive subjects, such as children and elderly. This
308 intraspecies uncertainty factor usually has a value of 10. This factor can be equally divided into a
309 toxicokinetic variability component with a default value of 3.16 [i.e., $(10)^{1/2}$], and a
310 toxicodynamic variability component also with a default value of 3.16, assuming these
311 components act independently.

312 The intraspecies uncertainty factor of 10 and the associated subfactors of 3.16 have been
313 justified for children based upon multiple studies that have compared the clinical response to
314 pharmaceutical agents in children versus adults as well as the toxic response to chemical agents
315 in younger versus older animals. (Burin, 1999; Dourson, 2002) For example, the National
316 Academy of Sciences Committee on Pesticides in the Diets of Infants and Children reviewed
317 several human and animal studies and concluded that the 10-fold intraspecies uncertainty factor

318 was sufficient to protect infants and children (Bruckner, 2000). Furthermore, comparison of the
 319 toxicokinetic data of 60 xenobiotics and the toxicodynamic data of 49 xenobiotics in adults,
 320 children, and other groups has shown the composite 10-fold factor covers the great majority of
 321 the population (Renwick, 1998). Further work is needed to determine whether the default
 322 uncertainty factors offer adequate protection for children, especially for inhaled exposure to
 323 gases and particles, and for children with lung disease, such as asthma or cystic fibrosis

324 The preponderance of current data indicate that a leachable below the Qualification
 325 Threshold is unlikely to cause acute or chronic noncarcinogenic toxicity, and in the absence of
 326 structural alerts for carcinogenicity or irritation should not require compound-specific risk
 327 assessment.

328 **Table 1. Bronchoconstrictor Concentrations in Asthmatics Relative to Occupational**
 329 **Short Term Exposure Limits (STELs) and RD50 Values**

Compound	STEL (mg/m ³)	RD50/1000 (µg/m ³)	Bronchoconstriction in Asthmatics	Reference
Nitrogen Dioxide	9.4	655	None at 753 µg/m ³	Tunncliffe <i>et al.</i> , 1994
Sulfur Dioxide	13	523	Range = 666 to 10500 µg/m ³ (20- to 1.2-fold below STEL)	Rubinstein <i>et al.</i> , 1990
Sulfuric Acid	3.0	NA	None at 46 µg/m ³ (65- fold below STEL) Some at 130 µg/m ³ (23- fold below STEL)	Avol <i>et al.</i> , 1990
Formaldehyde	2.45	39	None at 3700 µg/m ³ for 3 hr (1.5 × STEL)	Sauder <i>et al.</i> , 1987
Toluene Diisocyanate	0.14	4.8	Most at >14 µg/m ³ (10- fold below STEL) A few at ≤7 µg/m ³ (≤20- fold below STEL)	O'Brian <i>et al.</i> , 1979

STEL = Short term exposure limit; RD50 = Concentration decreasing respiratory rate by 50% in mice; NA = Not available.

331
332 **IV. Application of Safety Thresholds in the Pharmaceutical Development Process for**
333 **OINDP**

334 In general, the use of safety thresholds is considered acceptable in cases where adequate
335 supporting data are available; the Division of Pulmonary and Allergy Products (DPAP) in FDA's
336 Center for Drug Evaluation and Research/Office of New Drugs has incorporated the application
337 of safety thresholds in the qualification process conducted for leachables and extractables in
338 OINDP over the last decade. It is recognized that the appropriate application of safety thresholds
339 has advantages, including a reduction in the unnecessary expenditure of animals, time, effort,
340 and money. This reduced expenditure may allow greater resources to be applied to drug
341 development areas that present more significant safety concerns.

342 Currently, no formal regulatory guidance on the safety evaluation of leachables and
343 extractables is available. In the absence of formal guidance, the DPAP developed an internal
344 practice which includes the following general approach: identification of the compound,
345 determination of the maximum daily human exposure based upon the proposed product
346 specification (e.g., amount of specific leachable in drug product, typically in units of ppm or
347 µg/canister), conduct of a structure activity relationship (SAR) assessment for
348 genotoxic/carcinogenic potential through use of published lists (Ashby *et al.*, 1989; Tennant and
349 Ashby, 1991) or software programs such as DEREK (Deductive Estimation of Risk from
350 Existing Knowledge, www.chem.leeds.ac.uk/luk/) or Multicase (www.multicase.com), and
351 review of available toxicology/safety data bases or conduct of toxicology studies as deemed
352 necessary, e.g., 14-90 day general toxicology, genetic toxicology. The final safety assessment

353 should be based on a consideration of the maximum expected daily human exposure, the
354 intended patient population, and the anticipated duration of use.

355 Specific considerations for the safety assessment of leachables and extractables in
356 OINDP include three primary components: systemic toxicity, local toxicity of the respiratory
357 tree, and mutagenic/carcinogenic potential. The DPAP identified a safety threshold for systemic
358 and local toxicity parameters based on an evaluation of the US EPA's IRIS and HEAST
359 databases (Risk Assessment Information System, Chemical Specific Toxicity Values. Database
360 contains information taken from the United States Environmental Protection Agency's (EPA's)
361 Integrated Risk Information System (IRIS), the Health Effects Assessment Summary Tables
362 (HEAST). www.risk.lsd.ornl.gov/tox/tox_values.shtml) and concluded that there is no significant
363 safety concern for inhaled chemicals with a maximum expected daily dose of 5 µg/day (100
364 ng/kg) or less. Therefore, no further toxicity data are needed in most cases when the maximum
365 expected daily human exposure is below the stated threshold.

366 The safety threshold for systemic toxicity was derived from an evaluation of 36
367 chemicals listed in the EPA database that were administered via the inhalation route and were
368 associated with systemic toxicity. The presumed safe dose derived from the reference
369 concentrations (RfC's) for these compounds were all \geq 100 ng/kg with three exceptions; the
370 three exceptions had a "safe" dose of 80 ng/kg. Considering the large safety factors (1,000 –
371 10,000) that are incorporated into the calculation of RfCs, a safety threshold of 100 ng/kg was
372 considered reasonable. The safety threshold for respiratory toxicity was derived from an
373 evaluation of 20 chemicals with inhalation data that produced respiratory tract toxicity. All but 4
374 of these chemicals had presumed safe daily inhalation exposures greater than 100 ng/kg based on
375 the RfCs, even after incorporation of large safety factors (300-1,000). Of note, all of the

376 compounds with a presumed safe dose less than 100 ng/kg had a structural alert associated with
377 respiratory irritation. These structural alerts include isocyanates, aldehydes, organic acids,
378 strained heterocyclic rings, and halogenated aromatic rings.

379 As described earlier, subsequent data analyses conducted by the PQRI Working Group
380 expanded the database evaluation to include the ATSDR and CAL EPA databases. The Working
381 Group also concluded that a threshold of 5 µg/day presented a negligible safety concern for non-
382 carcinogenic effects, and recommended a qualification threshold of 5 µg/day (100 ng/kg/day, 50
383 kg person). Thus, the threshold recommended by the Working Group is in agreement with
384 current DPAP practice.

385 There are some exceptions to the use of the above described threshold approach for
386 leachables and extractables in inhalation products, and these include compounds identified as
387 respiratory irritants and sensitizers, and those that present a known or suspected genotoxic or
388 carcinogenic potential. With regard to respiratory irritants and sensitizers, chemicals should be
389 evaluated for structural alerts associated with irritation or sensitization. This determination is
390 especially important when considering the indicated population for a given product. Most
391 inhalation products approved to date are indicated for treatment of pulmonary diseases such as
392 asthma. These patients are already considered to have a compromised respiratory function and
393 may be more sensitive to the effects of irritants or sensitizers. If a compound is considered to
394 have an irritant or sensitizing potential, patient risk should be assessed on a case-by-case basis
395 after evaluating the available information for the specific compound. Additionally, the clinical
396 experience with the drug product should be evaluated for evidence of any adverse effects. If no
397 concern is identified for irritancy or sensitization, the safety qualification threshold for systemic
398 and local toxicity of 5 µg/day is appropriate. For anticipated clinical exposures greater than 5

399 $\mu\text{g}/\text{day}$, safety qualification should be conducted for systemic and local toxicity, as described
400 later in this section.

401 The DPAP currently has no formal policy or practice with regard to a safety threshold for
402 leachables or extractables with an identified or suspected genotoxic or carcinogenic potential.
403 As discussed earlier, the PQRI Working Group proposed a SCT of $0.15 \mu\text{g}/\text{day}$, a threshold
404 derived from calculated risk-specific doses of genotoxic (SAL-positive) carcinogens from the
405 CPDB and considered to be a dose below which a leachable would present negligible concern for
406 adverse carcinogenic and noncarcinogenic effects. The proposed SCT for negligible
407 carcinogenic effects expands on the DPAP's previous use of thresholds that focused primarily on
408 general toxicological effects. The PQRI proposal is, however, similar to that described
409 previously by FDA's Center for Food Safety and Nutrition for the safety assessment of food
410 contact materials (FDA, 2002), and a similar proposal has been made to support safety thresholds
411 for genotoxic impurities (Müller *et al.*, 2006). The proposed approach is supported by a large
412 database, and the applied cancer risk of 10^{-6} is considered appropriate due to the nature of the
413 chemicals that are commonly encountered as leachables and to the lack of any benefit derived
414 from their presence. Notably, high potency carcinogens (e.g., nitrosamines, PAHs) are excluded
415 from this threshold approach. While the PQRI Working Group recommendation has not yet
416 been formally accepted by the FDA, the proposal is considered in DPAP's safety evaluation of
417 suspected or known carcinogenic leachables and extractables.

418 Leachables and extractables are considered adequately qualified for genotoxic or
419 carcinogenic potential if they are demonstrated to produce negative results in genotoxicity and/or
420 carcinogenicity assays or, in cases where these data are not available, if they lack structural alerts
421 for these endpoints. When no concern for genotoxic or carcinogenic potential is identified, a

422 qualification threshold of 5 µg/day is appropriate in the absence of supporting general toxicology
423 data and an identified potential for respiratory irritation or sensitization. If a leachable or
424 extractable is a known or suspected genotoxin or carcinogen, appropriate tests should be
425 conducted or a rationale provided to alleviate this concern. Alternatively, consideration should
426 be given towards reducing the drug product specification to a level associated with the PQRI
427 Working Group recommended SCT of 0.15 µg/day. If the compound is a known carcinogen, the
428 product specification should be set to a level associated with a cancer risk of less than or equal to
429 10^{-6} .

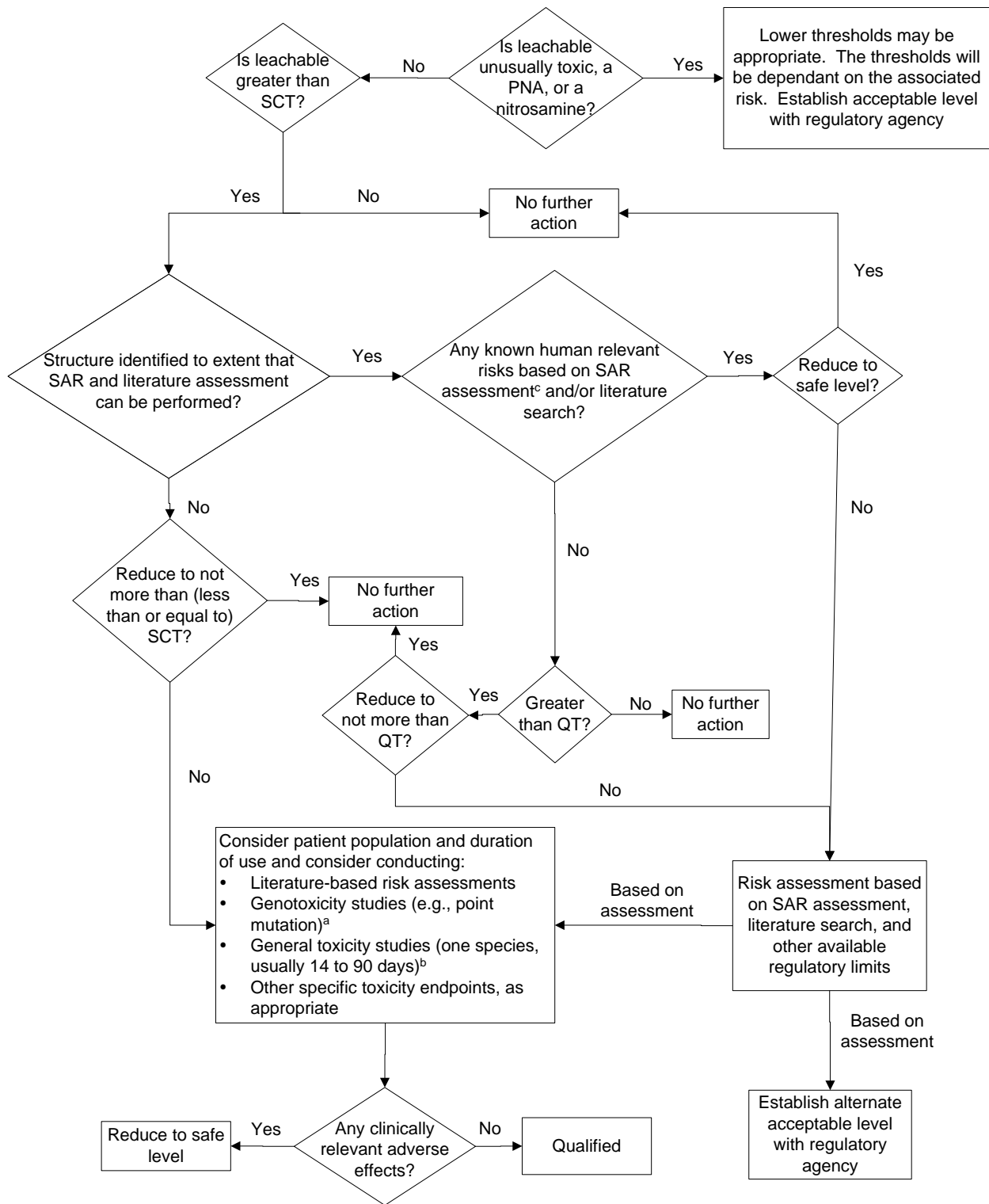
430 In general, when adequate safety data are available to support a proposed product
431 specification, conduct of a compound-specific risk assessment rather than a threshold-based
432 evaluation is recommended. It is anticipated that, in most cases, higher product specifications
433 would be supported from a safety standpoint when data are available to support a compound-
434 specific risk assessment than would be through use of a threshold-based approach. In cases
435 where the initial safety evaluation demonstrates a lack of genotoxic/carcinogenic or airway
436 sensitization risk and the proposed specification is below the QT, additional risk assessment is
437 not necessary.

438 In cases where the maximum expected human exposure to a leachable is expected to
439 exceed DPAP's qualification threshold of 5 µg/day, safety qualification for general toxicity
440 concerns may be provided through evaluation of published toxicity data or relevant regulatory
441 exposure limits such as US EPA air quality standards, or through the conduct of inhalation
442 toxicology studies of an appropriate duration (e.g., at least 90 days duration for chronic
443 indications). In some cases, data for chemicals with well-characterized toxicity profiles that

444 have a high degree of structural similarity to a leachable/extractable for which limited safety data
445 are available may be considered.

446 When toxicology data are used to support proposed product specifications, the most
447 relevant data should be considered. For example, if data are available from studies using both
448 oral and inhalation administration, the data derived from the inhalation studies are usually
449 considered to be most relevant. Safety margins for anticipated human exposures are calculated
450 based upon the NOAELs in animal studies. Generally, a 10-fold safety factor is applied for
451 cross-species extrapolation. In cases where safety data are only available from studies using the
452 oral route of administration, an additional 100-fold safety factor is applied, based on an
453 evaluation of a subset of the EPA HEAST database for which data were available following both
454 oral and inhalation administration. For this subset of chemicals, the presumed safe inhalation
455 doses derived from the RfCs were up to 100-fold lower than the identified reference doses
456 (RfDs) after conversion to a mg/kg/day dose. Therefore, a 1,000-fold safety factor (10 x 100) is
457 typically applied when using animal data from oral studies to support human inhalation use.

458 The PQRI Leachables and Extractables Working Group's proposed process for safety
459 qualification of leachables incorporating use of the safety concern and qualification thresholds, is
460 shown in decision tree format in Figure 3. The decision tree supports FDA recommendations for
461 application of safety thresholds. Note that in some cases, decreasing the level of a leachable to
462 not more than the threshold can be simpler than providing safety data. Alternatively, adequate
463 data could be available in the scientific literature to qualify a leachable. If neither is possible,
464 additional safety testing should be considered. The studies considered appropriate to qualify a
465 leachable will depend on a number of factors, including the patient population, daily dose, and
466 duration of drug administration.



467 **Figure 3.** Decision Tree for Identification and Qualification. (a) If considered desirable, a
 468 minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point
 469 mutations, in vitro, is considered an appropriate minimum screen. (b) If general toxicity studies
 470 are desirable, one or more studies should be designed to allow comparison of unqualified to
 471 qualified material. The study duration should be based on available relevant information and
 472 performed in the species most likely to maximize the potential to detect the toxicity of a
 473 leachable. On a case-by-case basis, single-dose studies can be appropriate, especially for single-
 474 dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days

475 would be considered appropriate. (c) For example, do known safety data for this leachable or its
476 structural class preclude human exposure at the concentration present?

477

478

479 The following case examples are presented to illustrate the safety qualification process.

480 Case 1. Bis-2-ethyl-hexyl sebacate (CAS RN 122-62-3)

481 The proposed product specification corresponded to a maximum daily human exposure of

482 9.1 µg/day (182 ng/kg/day for a 50 kg individual). The most relevant toxicity study identified

483 for this compound was a published chronic dietary study in rats in which a NOEL of 200 mg/kg

484 was observed. This dose corresponds to an acceptable human inhalation exposure of 0.2

485 mg/kg/day (200,000 ng/kg/day) after including a 1,000-fold safety factor for cross-species

486 extrapolation and for the use of data derived from oral administration to support inhalation use.

487 Even after incorporation of this safety factor, a greater than 1,000-fold safety margin for bis-2-

488 ethyl-hexyl sebacate was present when comparing the acceptable human daily exposure to the

489 maximum anticipated human exposure associated with the proposed product specification.

490 Case 2. 4-toluenesulfonamide (CAS RN 70-55-3)

491 The proposed product specification corresponded to a maximum daily human exposure of

492 60 µg/day (1200 ng/kg/day). In this case, the sponsor provided no supporting rationale for the

493 proposed specification. However, a review of the literature indicated that only acute toxicity

494 data were available. In this case, the DPAP requested that the sponsor lower the product

495 specification to a level that corresponded to the Division's safety qualification threshold of 5

496 µg/day or provide adequate toxicology data, such as a 90 day inhalation toxicity study, to support

497 their proposed product specification.

498 Case 3. Acenaphthene (CAS RN 83-32-9)

499 The proposed product specification corresponded to a maximum daily human exposure of
500 0.067 µg/day (1.33 ng/kg/day). As in the previous case, only acute toxicity data were available.
501 However, a State of Minnesota drinking water standard for acenaphthene is set at 400 µg/L (U.S.
502 EPA Office of Water, Federal-State Toxicology and Risk Analysis Committee (FSTRAC)
503 (November 1993). Summary of State and Federal Drinking Water Standards and Guidelines).
504 This standard corresponds to an acceptable daily inhalation exposure of 160 ng/kg assuming a
505 daily intake of 2 liters/day, a 50 kg BW, and incorporation of a 100-fold safety factor for the use
506 of oral data to support inhalation use. The calculated acceptable inhalation exposure for humans
507 provided a greater than 100-fold safety margin, when compared to the maximum daily human
508 exposure to acenaphthene through use of the drug product at the sponsor's proposed
509 specification. In addition, the anticipated human exposure was well below the DPAP's safety
510 qualification threshold of 5 µg/day.

511 Case 4. Nitrosamines

512 Nitrosamines can be present in certain rubber components of inhalation devices and are
513 known carcinogens. In one product, six species were identified at various levels. The
514 carcinogenic risk assessment was based on total nitrosamine exposure using the slope factor
515 calculated for NMDA. A maximum human daily exposure of up to 0.04 ng/kg, a level
516 associated with a cancer risk estimate of 10^{-5} , was accepted based on the overall risk-benefit
517 analysis and technological considerations, namely, the inability to manufacture rubber
518 components that do not potentially leach nitrosamine compounds. Although the Division
519 allowed a level that corresponded to a cancer risk estimate of 10^{-5} , DPAP encourages sponsors to
520 continue to reduce the potential for exposure and to strive to develop methods to eliminate the
521 presence of nitrosamine compounds.

522 As stated previously, issues arising from the need for adequate safety qualification for
523 leachables and extractables can often delay the approval of drug products. Therefore, some
524 consideration should be given to addressing these issues earlier in product development or
525 providing more substantive qualification information. Some ways in which the safety
526 qualification process can be improved include the selection of materials to limit the number and
527 level of potential leachables, the use of pre-extraction methods to lower potential exposures, and
528 the submission of a clear rationale to support the safety of proposed product specifications.
529 Often, the DPAP receives submissions containing only the proposed drug product specifications
530 for a given leachable or extractable with no supporting rationale. It must be stressed that
531 submission of an adequate supporting rationale often leads to a more efficient and expeditious
532 review of a submission, with regard to the safety qualification of leachables and extractables.

533 **V. Conclusion**

534 The safety thresholds for leachables in OINDP developed by the PQRI Leachables and
535 Extractables Working Group – a safety concern threshold of 0.15 µg/day and a qualification
536 threshold of 5 µg/day – provide scientifically sound guideposts for industry and regulators to
537 ensure, with a high degree of confidence, the safety of patients using these drug products. These
538 thresholds were developed taking into consideration accepted safety thresholds for indirect food
539 additives, impurities in drug substances, drug products, residual solvents, and genotoxic
540 impurities in drug products. A scientifically sound process using well-established databases, risk
541 assessment approaches, and literature information relevant to inhalation products was used to
542 derive the thresholds. The Working Group also developed a recommended safety qualification
543 process that incorporates application of the SCT and QT. This process supports FDA's
544 recommended processes for application of safety thresholds.

545 The PQRI thresholds and qualification process were developed with FDA regulatory
546 support, and are expected to be used in pharmaceutical development programs and by regulators
547 assessing drug applications. These scientifically justified thresholds will have a significant
548 positive impact on the OINDP development and regulatory review process by removing
549 uncertainty in the development process and directly linking safety with quality of OINDP.

550 **VI. Acknowledgements**

551 The authors thank the Product Quality Research Institute and the International
552 Pharmaceutical Aerosol Consortium on Regulation and Science, and their member organizations,
553 for support of this work.

554

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